

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re patent application of: Alexandros Makriyannis

Application No.: 10/790,498 Examiner: STOCKTON, L. L.

Filing Date: 3/1/2004 Group Art Unit: 1626

For: Novel Pyrazole Analogs Acting On Cannabinoid Receptors

To: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Sir:

**RESPONSE TO RESTRICTION OR ELECTION REQUIREMENT**

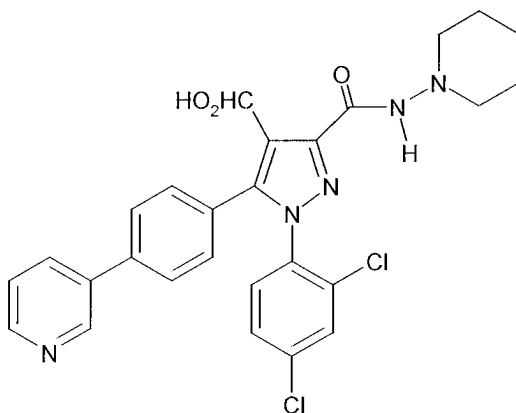
The Office Communication dated 8/3/2006 for the above application imposed a two-way restriction requirement between the asserted inventions of Groups:

- I. claims 1-14, drawn to products
- II. claims 15-20, drawn to methods of use

In order to strictly comply with the Examiner's requirement in the above restriction requirement, and without agreeing to the propriety of the restriction requirement, Applicant elects the invention of Group 1, including claims 1-14 drawn to products.

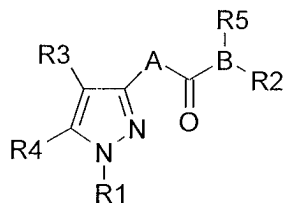
• **The elected species**

Applicant selects the following single species within elected Group I.



The selected species is supported by the specification at, for example pages 2 to 23 at least as follows:

The structure of compound formula I:



wherein:

I

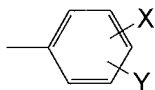
A is a direct bond;

B is N;

R1 is  $-(CH_2)_n-Z$ ,

n is 0,

Z is



wherein X and Y each independently comprise halogen.

R2 is a heterocyclic ring having about 4 to about 7 members.

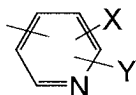
R5 is H.

R3 is  $CH_2OH$ .

R4 is  $-Ph-(CH_2)_n-Z$ ,

n is 0,

Z is selected from

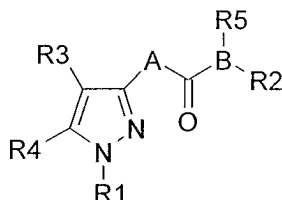


wherein X and Y each independently comprise H.

• **The family proposed for examination in this application**

Applicant proposes the following family within the elected group for examination.

The structure of compound formula I:



wherein:

A is a direct bond;

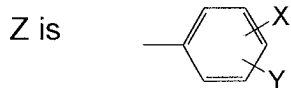
B is N;

R1 is  $-(CH_2)_n-Z$ .

n is 0.

Z is an aromatic ring having about 5 to about 7 ring members or an aromatic ring having about 5 to about 7 ring members substituted on at least one available ring atom by an alkyl group; and wherein the connecting point between the  $-(CH_2)_n$ -group and the Z group can be any available ring carbon atom; or

Z is a 6 member aromatic ring or a substituted 6 member aromatic ring; and wherein the connecting point between the  $-(CH_2)_n$ - group and the Z group can be any available ring carbon atom; or



wherein X and Y each independently comprise H, halogen,  $N_3$ , NCS, CN,  $NO_2$ ,  $NX_1X_2$ ,  $OX_3$ , OAc, O-acyl, O-aryl, NH-acyl, NH-aryl, CHO,  $CF_3$ ,  $COOX_3$ ,  $SO_3H$ ,  $SO_2NX_1X_2$ ,  $CONX_1X_2$ , alkoxy, alkylmercapto, alkylamino, di-

alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms methylene dioxy.

$X_1$  and  $X_2$  each independently comprise H or alkyl, or

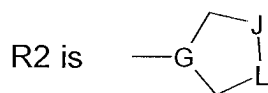
$X_1$  and  $X_2$  together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

$X_1$  and  $X_2$  together comprise part of an imide ring having about 5 to about 6 members.

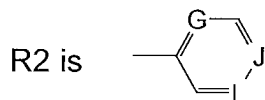
$X_3$  comprises H, alkyl, hydroxyloweralkyl or alkyl- $NX_1X_2$ .

$X_4$  comprises H or alkyl.

R2 is selected from a carbocyclic ring having about 4 to about 7 members, a heterocyclic ring having about 4 to about 7 members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring; or

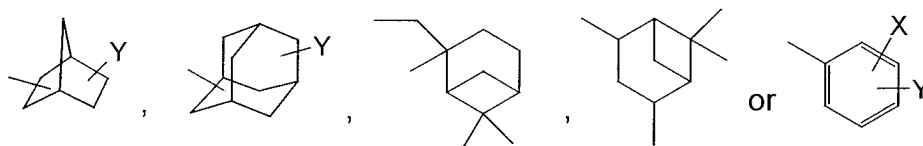


wherein G comprises CH or N, and L and J each independently comprise  $(CH_2)_n$ , O, NH or S. n is an integer from 0 to about 7; or



wherein G, L and J each independently comprise CH or N; or

R2 is selected from



wherein X and Y each independently comprise H, halogen, N<sub>3</sub>, NCS, Ph (phenyl), CN, NO<sub>2</sub>, NX<sub>1</sub>X<sub>2</sub>, OX<sub>3</sub>, OAc, O-acyl, O-aryl, NH-acyl, NH-aryl, CHO, CF<sub>3</sub>, COOX<sub>3</sub>, SO<sub>3</sub>H, SO<sub>2</sub>NX<sub>1</sub>X<sub>2</sub>, CONX<sub>1</sub>X<sub>2</sub>, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X<sub>1</sub> and X<sub>2</sub> each independently comprise H or alkyl, or

X<sub>1</sub> and X<sub>2</sub> together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X<sub>1</sub> and X<sub>2</sub> together comprise part of an imide ring having about 5 to about 6 members.

X<sub>3</sub> comprises H, alkyl, hydroxyloweralkyl or alkyl-NX<sub>1</sub>X<sub>2</sub>; or

R2 is selected from a carbocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms or a heteroaromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms.

R5 is H or alkyl;

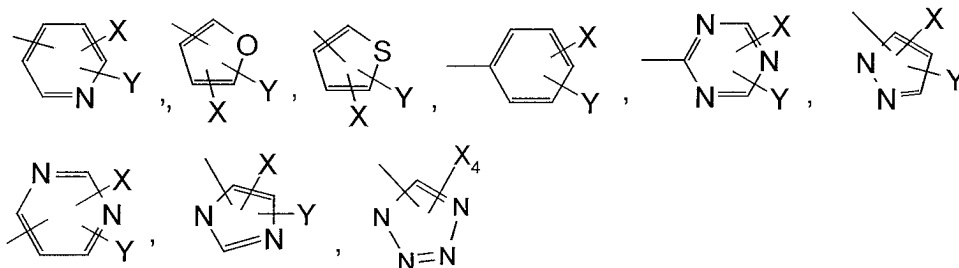
R3 is CN, CH<sub>3</sub> or CH<sub>2</sub>OH;

R4 is -Ph-(CH<sub>2</sub>)<sub>n</sub>-Z.

n is 0.

Z is selected from an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -(CH<sub>2</sub>)<sub>n</sub>- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from



wherein X and Y each independently comprise H, halogen, N<sub>3</sub>, NCS, CN, NO<sub>2</sub>, NX<sub>1</sub>X<sub>2</sub>, OX<sub>3</sub>, OAc, O-acyl, O-aryl, NH-acyl, NH-aryl, alcohol, CHO, CF<sub>3</sub>, COOX<sub>3</sub>, SO<sub>3</sub>H, SO<sub>2</sub>NX<sub>1</sub>X<sub>2</sub>, CONX<sub>1</sub>X<sub>2</sub>, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms) methylene dioxy.

X<sub>1</sub> and X<sub>2</sub> each independently comprise H or alkyl, or

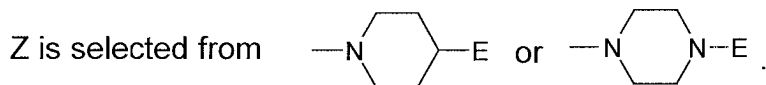
X<sub>1</sub> and X<sub>2</sub> together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X<sub>1</sub> and X<sub>2</sub> together comprise part of an imide ring having about

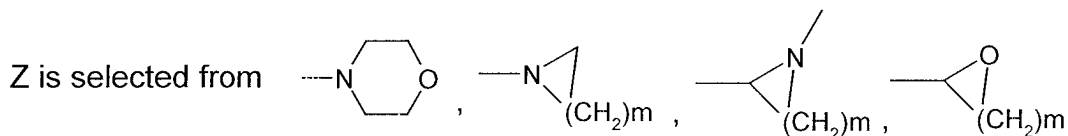
5 to about 6 members.

X<sub>3</sub> comprises H, alkyl, hydroxyloweralkyl or alkyl-NX<sub>1</sub>X<sub>2</sub>,

X<sub>4</sub> comprises H or alkyl; or



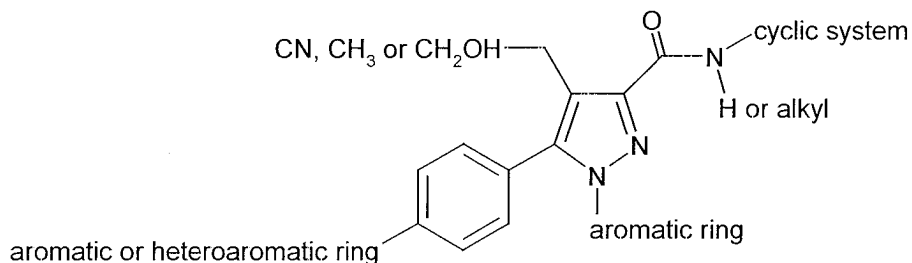
wherein E is selected from a C1 to about C4, linear or branched alkyl group, a phenyl group, a substituted phenyl group, a benzyl group or a substituted benzyl group; or



wherein m is an integer from 1 to about 5.

- **The family proposed for examination in this application has unity of invention**

Each of the compounds in the proposed family will share the following substantial common structure:



The Court of Appeals for the Federal Circuit, in the case of In re Watkinson, 14 USPQ2d 1407, 1409 (Fed. Cir. 1990), stated, with emphasis in original:

Under In re Weber, 580 F.2d 455, 458, 198 USPQ 328, 332 (CCPA 1978)

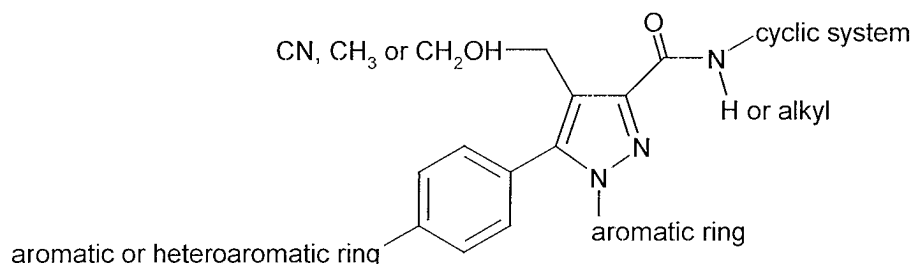
and In re Haas, 580 F.2d 461, 464, 198 USPQ 334, 336 (CCPA 1978), it is *never* proper for an Examiner to reject a Markush claim under 35 U.S.C. §121. Section 121 simply does not authorize such a rejection.

The MPEP in section 803.02, acknowledging the Court decisions of In re Weber, and In re Haas states: "it is improper for the Office to refuse to examine that which Applicants regard as their invention, unless the subject matter in a claim lacks unity of invention." That section of the MPEP goes on to illustrate the examination of an elected species of a Markush claim followed by, in the proper circumstances, examination of the *non-elected species*.

Under the Court precedent of *In re Harnish* and *Ex parte Hozumi* cited by MPEP section 803.02, with bracketed text added, "unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility.

The compounds within the Markush group of Applicant's proposed family (1) share a common utility: the compounds are believed to have binding affinity for both cannabinoid receptors with a preferential binding affinity for the CB1 receptor.

The compounds within the Markush group of Applicant's proposed family (2) share a substantial structural feature disclosed as being essential to that utility: the compounds share the following core structure:



Applicant's proposed family for examination recites similar moieties for the



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Attorney Docket: UCONAP/226/US

substituent positions. For example, R1 recites a small family of aromatic ring or substituted aromatic ring structures. R2 recites a small family of single or multiple ring structures. R3 has been substantially limited to CN, CH<sub>3</sub> and CH<sub>2</sub>OH. R4 has also been substantially limited to recite a phenyl ring linked to a small family of unsubstituted or substituted aromatic and heteroaromatic ring structures. Thus, Applicant's proposed family has unity of invention and is a proper subject for examination in this application.

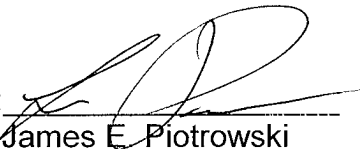
Further, Applicant's proposed family provides a rational, clear and concise basis from which to file and prosecute the present application as well as subsequent divisional applications.

Applicant will amend the claims to reflect the examined family once that family has been established on the record.

Respectfully submitted,

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